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## Origin of chiral pharmacology: stereochemistry in metalloprotease inhibition.

**Kim DH.**

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The stereospecificity shown by a wide variety of inhibitors that are effective for carboxypeptidase A (CPA), a representative zinc protease is analyzed on the basis of inhibitor type. In cases of ground state analog inhibitors and transition state analog inhibitors, the stereoisomers having the stereochemistry that corresponds to stereochemistry of substrate are more potent, but in the case of irreversible inhibitors including mechanism-based inactivators the preferred inhibitory stereochemistry cannot be predicted simply from the substrate stereospecificity. The Ogston's three point fit concept may be of great value in understanding the inhibitory stereochemistry of reversible competitive inhibitors. On the other hand, the stereochemistry of irreversible inhibitors may possibly be predicted on the ground of the transition state structure that plays a critical role in the inactivation pathway.

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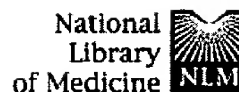
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Tutorial

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**Mechanistic insight into the inactivation of carboxypeptidase A by alpha-benzyl-2-oxo-1,3-oxazolidine-4-acetic acid, a novel type of irreversible inhibitor for carboxypeptidase A with no stereospecificity.**

**Chung SJ, Chung S, Lee HS, Kim EJ, Oh KS, Choi HS, Kim KS, Kim YJ, Hahn JH, Kim DH.**

Center for Biofunctional Molecules and Division of Molecular and Life Sciences, Pohang University of Science and Technology, San 31 Hyojadong, Pohang 790-784, Korea.

On the basis of the active site topology and enzymic catalytic mechanism of carboxypeptidase A (CPA), a prototypical zinc-containing proteolytic enzyme, alpha-benzyl-2-oxo-1,3-oxazolidine-4-acetic acid (1), was designed as a novel type of mechanism-based inactivator of the enzyme. All four possible stereoisomers of the inhibitor were synthesized in an enantiomerically pure form starting with optically active aspartic acid, and their CPA inhibitory activities were evaluated to find that surprisingly all of the four stereoisomers inhibit CPA in a time dependent manner. The inhibited enzyme did not regain its enzymic activity upon dialysis. The inactivations were prevented by 2-benzylsuccinic acid, a competitive inhibitor that is known to bind the active site of the enzyme. These kinetic results strongly support that the inactivators attach covalently to the enzyme at the active site. The analysis of ESI mass spectral data of the inactivated CPA ascertained the conclusion from the kinetic results. The values of second-order inhibitory rate constants ( $k(\text{obs})/[I](0)$ ) fall in the range of 1.7-3.6 M<sup>-1</sup> min<sup>-1</sup>. The lack of stereospecificity shown in the inactivation led us to propose that the ring cleavage occurs by the nucleophilic attack at the 2-position rather than at the 5-position and the ring opening takes place in an addition-elimination mechanism. The tetrahedral transition state that would be generated in this pathway is thought to be stabilized by the active site zinc ion, which was supported by the PM3 semiempirical calculations. In addition, alpha-benzyl-2-oxo-1,3-oxazolidine-5-acetic acid (18), a structural isomer of 1 was also found to inactivate CPA in an irreversible manner, reinforcing the nucleophilic addition-elimination mechanism. The present study demonstrates that the transition state for the inactivation pathway

plays a critical role in determining stereochemistry of the inactivation.

PMID: 11559199 [PubMed - indexed for MEDLINE]

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